REMARKS

Claim 36 is currently pending in this application and is in independent form. Claim 36 is believed to be in condition for allowance. Removal of the rejection and allowance of claim 36 is respectfully requested.

Claim 36 is directed to a method of preparing an osteogenic protein fraction, extracting demineralized bone matrix with a solution of at least one chaotropic agent; removing high molecular weight proteins which exceed 300 kDA from the extract by ultrafiltration with a 300 kDA membrane to produce a lower molecular weight fraction; subjecting the lower molecular weight fraction to heparin affinity chromatography under conditions which first favor the binding and then the elution of a purified heparin affinity fraction containing the osteogenic protein fraction; subjecting the heparin affinity fraction to hydroxyapatite chromatography under conditions which first favor the binding and then the elution of a purified osteogenic protein fraction; and exchanging the purified osteogenic protein fraction into a solvent suitable for human medical use. The chaotropic agent is selected from the group consisting of urea and guanidinium salts to produce an extract.

Claim 36 is rejected under 35 U.S.C. §103(a) as being obvious over either Scott et al. (1994, The Anatomical Record 238:23-30) (hereinafter "the Scott reference") or Yoshimura et al. (1993, Biol. Pharm. Bull. 16(5):444-447) (hereinafter "the Yoshimura reference") in view of United States Patent No. 4,968,590 to Kuberasampath et al. (hereinafter "the Kuberasampath patent").

The Scott reference is directed toward a method of isolated osteoinductive proteins from intramembraneous (IM) proteins from bones.

The Yoshimura reference is directed toward the purification of water-soluble bone-inductive protein from bovine demineralized bone matrix. The purification steps include ultrafiltration, dialysis, affinity chromatography on heparin-Sepharose and gel chromatography on Sephacryl S-200.

The Kuberasampath patent teaches hydroxyapatite chromatography after heparin affinity chromatography.

Applicant asserts that the claimed invention is not obvious over the cited prior art. An Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing "(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004) ;MPEP 2144.05(III). Not only does the prior art teach away from the claimed invention, but also the claimed method of preparing an osteogenic protein fraction using a 300 kDA membrane provides new and unexpected results relative to the Scott reference or the Yoshimura reference in view of the Kuberasampath patent; therefore, the claimed invention is not obvious over the cited prior art.

First, the prior art teaches away from the use of a 300 kDA filter. The protein of the claimed invention is filtered by a 300 kDA membrane. Specifically, the claimed invention utilizes a 300 kDA membrane to remove high molecular weight proteins which exceed 300 kDA from the extract by ultrafiltration. Proteins having molecular weights of more than 300 kDA are removed at the beginning of the claimed method prior to the chromatographic steps in order to improve the yield obtained in the subsequent heparin affinity and hydroxyapatite chromatography steps. The prior art does not teach the method of the claimed invention which utilizes a 300 kDA membrane for ultrafiltration. In fact, the Scott and the Yoshimura references utilize a 100 kDA membrane to isolate proteins having weights below 100 kDA and the Kuberasampath patent does not teach removing high molecular weight portions at all. The Applicant asserts that the ultrafiltration kinetic effects associated with the use of a 100 kDA filter (as disclosed in the Scott and Yoshimura references) to retain protein material having a mass of above 100 kDA results in the retention of lower molecular weight material in the retentate and a resultant loss of bone morphogenic protein. [Duneas Declaration, paragraph 6]. For at least the aforementioned reasons, the use of a 100 kDA membrane to isolate proteins having weights below 100 kDA, teaches away from the claimed method of preparing an osteogenic protein

fraction using a 300 kDA membrane.

Next, the claimed method of preparing an osteogenic protein fraction using a 300 kDA membrane provides new and unexpected results relative to the Scott reference or the Yoshimura reference in view of the Kuberasampath patent for at least the following reasons. First, the method of preparing an osteogenic protein fraction using a 300 kDA reduces transmembrane pressures; reduces the number of passes of the extract over a membrane; reduces the time necessary to complete ultrafiltration; and reduces the need for interventions to minimize fouling of the column by collagens and collagen aggregates. [Duneas Declaration, paragraph 7]. These limitations, which are overcome by the method of the claimed invention, are all associated with the methods taught and suggested by the Scott reference or the Yoshimura reference or the Kuberasampath patent. [Duneas Declaration, paragraph 7].

Additionally, the claimed method of preparing an osteogenic protein fraction using a 300 kDA membrane produces four times more protein than that produced by the method of the Kuberasampath patent, and an estimated two-fold more protein than when using a 100 kDA membrane. [Duneas Declaration, paragraph 5].

Finally, the claimed method of preparing an osteogenic protein fraction using a 300 kDA membrane produces a higher recovery of bound BMP than the method of the prior art. [Duneas Declaration, paragraph 6; Figs. 2a, 2b, and 2c]. For example, the claimed method recovers on average 41% of the total BMP in the original raw material.

For at least the aforementioned reasons, the claimed method of preparing an osteogenic protein fraction using a 300 kDA membrane provides new and unexpected results relative to the Scott reference or the Yoshimura reference in view of the Kuberasampath patent.

CONCLUSION

For the foregoing reasons, Applicant submits that the Scott and Yoshimura references neither teach nor suggest the use of a 300 kDA filter in order to isolate the osteogenic protein fraction of the claimed invention and that the method of the present invention is accordingly both novel and nonobvious in view of the disclosures of Kuberasampath, Scott and Yoshimura. Reconsideration of the rejections and allowance of claim 36 is respectfully requested.

Respectfully submitted,

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